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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
BRUNOVSKIS,P	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/051,034	Applicant(s) McKenzie et al.
	Examiner Peter Brunovskis	Group Art Unit 1632

☒ Responsive to communication(s) filed on Nov 6, 2000, Nov. 20, 2000 and July 14, 2000

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-25 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-25 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☒ The proposed drawing correction, filed on 7/14/00 is ☐ approved ☒ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

The responses filed 7/14/00, 11/06/00, 11/20/00 have been entered. Amendment of claims 1-11, 13-21, and 23-25 is acknowledged. Claims 1-25 are pending in the instant application. Applicant's arguments filed 11/06/00 will only be considered to the extent that they apply to the pending claims; arguments directed to any other subject matter is considered moot.

Drawings

The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on 7/14/00 have been disapproved. Addition of the number "6" for GT and gt-HT and "8" for HT and ht-GT is not consistent with the rest of the numbering. For example, if the aa 1-8 segment of HT was fused to the aa 6-359 segment of GT (to create ht-GT) it would not logically follow that ht-GT would have a TM segment bounded by the numbers 8-23 and a catalytic domain terminating in 359. Instead, the total length of ht-GT would be expected to be 361 amino acids, while that of gt-HT would be expected to be 363 amino acids in length. Another way to depict the constructions would be one not dependent on the numbers so much as to more clearly denote (hatched boxes etc) the origin the "CYTO" region and the "TM-STEM-CATALYTIC" region.

Additionally in Fig. 6, the designated SEQ ID NOs do not match the SEQ ID NOs in the SEQUENCE LISTING. First, the drawing newly marked as SEQ ID NO:1 actually depicts two

sequences, SEQ ID NO:1 and -2. The drawing newly marked as SEQ ID NO:2 actually depicts the two sequences set forth in the SEQUENCE LISTING as SEQ ID NOs: 3 and -4.

Appropriate correction is required.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claims 19 and 25 reciting "which cause it to be recognised as non-self by the recipient" and "wherein the carbohydrate is recognized as non-self by a species", respectively, both lack proper antecedent basis. The closest the specification comes to reciting this limitation is on p. 7, line 18-20: "Preferably said carbohydrate is capable of *stimulating* recognition of the cell as "non-self" by the immune system of an animal". The statements immediately following this passage (e.g. p. 7, lines 20-23 and p. 8, lines 11-18) are much more conservative than the recitations of claims 19 and 25.

Claim Objections

Newly amended claim 11 has not been entered, because the amendment to the claim is not in accordance with 37 CFR 1.121(a)(2)(ii) which states:

> (ii) Claim cancellation or rewriting: A claim may be amended by directions to cancel the claim or by rewriting such claim with underlining below the matter added and brackets around the matter deleted. The rewriting of a claim in this form will be construed as directing the deletion of the previous version of that claim. If a previously rewritten claim is again rewritten, underlining and bracketing will be applied relative to the previous version of

> the claim, with the parenthetical expression "twice amended," "three times amended," etc., following the original claim number. The original claim number followed by that parenthetical expression must be used for the rewritten claim. No interlineations or deletions of any prior amendment may appear in the currently submitted version of the claim. A claim canceled by amendment (not deleted and rewritten) can be reinstated only by a subsequent amendment presenting the claim as a new claim with a new claim number.

Newly amended claim 11 recites a nucleic acid "which encodes the NH_2 terminal cytoplasmic tail of GT attached to the transmembrane, stem and catalytic domains of Ht" in lines 1 and 2 which replaces "which encodes gtHT as defined herein" as filed in the original disclosure. However, the newly amended claim does not provide "which encodes gtHT as defined herein" in brackets nor is "which encodes the NH_2 terminal cytoplasmic tail of GT attached to the transmembrane, stem and catalytic domains of Ht" underlined (e.g. ...wherein the [recombinant nucleic acid] compound can be packaged...).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 16-25 remain rejected under 35 U.S.C. 112, second paragraph, for the reasons of record set forth in the Office Action of 3/09/00 and for the reasons set forth below as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 17-19 (and dependent claims) remain indefinite in their recitation of "a second glycosyltransferase" since it is unclear whether the "second glycosyltransferase" is obligated to encode a different enzyme, or whether it can embrace a different isoform relative to the "first" enzyme, or whether it can encompass the same enzyme from a different animal source, for example. Applicant's arguments filed 11/06/00 have been fully considered but they are not persuasive. The response contends that "the term 'resulting in reduced levels of a product from said second glycosyltransferase' clearly indicates that the second glycosyltransferase must be a different enzyme to the first glycosyltransferase" (p. 8). This argument is not persuasive because use of a second isoform (or species-type) as "second glycosyltransferase" would meet the limitations of the claim. However, when read in light of the specification, the claimed subject matter appears to be drawn to a chimeric enzyme comprising two different *types* of glycosyltransferases.

Claims 1, 18, and 19 (and dependent claims) remain indefinite in their recitation "located in an area of the cell where it is able to compete for substrate" since the nature of the competition has not been defined (e.g. is it direct, indirect etc.), nor the location of the "second glycosyltransferase". Applicants have failed to address the specific grounds for rejection as set forth in the previous Office Action. Although the response claims that the competition is a direct competition for substrate, this is not reflected in the recitation of the claimed subject matter.

Claims 3, 5, 8, and 10 are indefinite in their recitation of the phrase "wherein the localization signal is based on, or is similar to that of..." since it is unclear how "based on, or similar to" is defined or what its metes and bounds are.

Claim 6 remains indefinite in its recitation of "galactosyl sulphating enzyme" and a "phosphorylating enzyme" since there is no evidence on record suggesting these enzymes are glycosyltransferases, nor are there any specific examples of such enzymes given that would qualify as glycosyltransferases. Applicant's arguments filed 11/06/00 have been fully considered but they are not persuasive because they fail to address the specific grounds for rejection as set forth in the previous Office Action. The response implicitly admits that a "galactosyl sulphating enzyme" and a "phosphorylating enzyme" are not glycosyltransferases, but state that "the catalytic domains of such enzymes can be used with localization signals in accordance with the invention, to target carbohydrates...or to selectively phosphorylate sugar molecules and that the catalytic domains of such enzymes provide another way for the concept of the invention to be applied" (p. 9). While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). "Galactosyl sulphating enzymes" and "phosphorylating enzyme" are not glycosyltransferases; as such they do not further limit their base claim (i.e. claim 1).

Claim 7 remains indefinite in its recitation of "originates from" since it is unclear how "originates from" is defined or what the structural relationship is between the mammal and the recited domains. "Originates from" implies or embraces an evolutionary relationship which

confuses the metes and bounds of the claim. Applicants arguments and amendments fail to address or obviate the grounds for rejection. Changing the phrase "and the localization signal each originates from a mammal..." to --and the localization signal are each from a mammal-- would obviate the rejection.

Claim 8 remains indefinite in its recitation of the "is intended to transform" in line 3, since there is insufficient antecedent basis for this limitation in the claim. Applicants arguments and amendments fail to address or obviate the grounds for rejection. Changing the phrase "the cell which the nucleic acid is intended to transform" to --the cell of claim 1-- would obviate the rejection. In addition, claim 8 remains indefinite in its recitation of "species" since it is unclear whether "species" refers to or is directed to the nucleic acid or the cell.

Claims 9 and 16 (and dependent claims) remain indefinite in their recitation of "Gal transferase" and "gal-transferase", respectively, since it is not clear whether the recitation of "Gal transferase" or "gal-transferase" is limited to the α (1,3)-galactosyltransferase described in the specification (p. 2, line 23) or whether it can encompass other galactosyltransferases, since the term "Gal-transferase" has been used in the art in a general way to refer to other *species* of "Gal-transferase", such as β (1,4)-galactosyltransferase, for example. Despite Applicants response which asserts that "claims 9 and 16 have been amended to further define Gal-transferase" (i.e. to further facilitate prosecution), the amendment to the claims fail to reflect this assertion or obviate the grounds for rejection. If Applicants intend to recite a Gal-transferase which catalyzes the production of an enzyme reactive with an antibody to thereby cause hyperacute rejection, they

should specify the *particular* genus or species of "Gal-transferase" that would meet the limitations of the claim. Additionally, by reciting "localization signal from Gal-transferase" the claim appears to suggest that "Gal-transferase" is directed to a *specific* Gal-transferase as opposes to "localization signal from a Gal-transferase".

Claim 23 (and dependent claims) is indefinite in its recitation of the phrase "nucleic acid that expresses a nucleic acid according to claim 1" since it is unclear what is meant by the use of "nucleic acid" twice (i.e. nucleic acid to express a nucleic acid) in accord[ance] with the nucleic acid according to claim 1. Further, the claim remains indefinite because it is unclear how "expression unit" is defined in this context, particularly since claim 23 recites an expression unit as being used to transform a cell, whereas claim 24 describes a retroviral producer cell as an example of an "expression unit according to claim 23".

Claim 25 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim. Applicants submit that the amendments to claim 25 render this rejection moot. This argument is not persuasive, because the claim does not clarify the structural metes and bounds of "expression unit" in accordance with the rejection previously applied to claim 23 (and dependent claims) and maintained herein.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 12-25 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office Action of 3/09/00 and for the reasons set forth below, because the specification, while being in principle enabling for *specific* chimeric glycosyltransferases, such as gtHT and pgtHT, it does not reasonably provide enablement for the broad scope of chimeric glycosyltransferases exemplified in claims 1, 6, 7, 8, and 17-19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments filed 11/06/00 have been fully considered but they are not persuasive. First, the response appears to be incomplete inasmuch as the arguments appear to be directed at just one of the grounds for rejection under lack of enablement--that dealing with uncertainties relating to localization signals. Uncertainties regarding localization signals constitute only *one* of the issues relative to the prima facie case for lack of enablement set forth in the Office Action of 3/09/00. The specification describes the use of functionally active chimeric enzymes comprising the amino terminal "tail" of porcine α-1,3-galactosyltransferase (GT) fused to the catalytic domains of human α-1,2-fucosyltransferase (HT; resulting in gtHT) or pig α-1,2-fucosyltransferase (resulting in pgtHT; Example 4, p. 21) or the amino terminal "tail" of HT fused to the catalytic domain of GT (resulting in htGT). However, the broadly recited claims cover

virtually any nucleic acid encoding a chimeric enzyme comprising a glycosyltransferase localization signal fused to a catalytic domain of a glycosyltransferase, galactosyl sulphating enzyme, or phosphorylating enzyme (e.g. kinase). The claimed subject matter requires the chimeric enzyme to carry a localization signal from a second glycosyltransferase "to compete for substrate" with a second glycosyltransferase (or galactosyl sulphating enzyme or phosphorylating enzyme) for the purpose of reducing the level of carbohydrate or product produced from said second glycosyltransferase (or other). The primary purpose of the invention described in the working examples is to reduce production of a carbohydrate associated with hyperacute rejection. However, the claims are broadly drawn to essentially any chimeric enzyme containing a heterologous localization signal designed to compete for some unspecified substrate with some unspecified second enzyme to reduce the levels of product ordinarily produced through the action of the second enzyme.

The response appears to traverse the notion that "uncertainties relating to localization signals" by referencing description of localization signals disclosed in the paragraph abridging pages 11 and 12 of the specification and in the article (Schwientek et al) set forth as in the 35 U.S.C. 102 rejection below. The fact that localization signals were described at the time the invention was made does not obviate the grounds for rejection set forth in the Office Action of 3/09/00. The claims recite nucleic acids encoding functional chimeric enzymes capable of reducing the level of carbohydrate or product produced from a second glycosyltransferase (or enzyme). However, the specification only teaches how to use chimeric enzymes such as gtHT

which is designed to help reduce hyperacute rejection. The specification does not teach how to make or use any other specific chimeric enzymes. Further, the specification does not teach or provide any other examples of carbohydrates or products whose reduction in the context of the asserted inventive "concept" would carry any practical utility. Upon close inspection of the Schwientek reference, the evidence of record reveals that the generic "concept" of the invention (e.g. as set forth in claim 1) was described by Schwientek before the date that the instant invention was filed (see sentence immediately before "Experimental Procedures on p. 3399 and middle of last paragraph, right column of p. 3404). It is not sufficient to merely claim some generic composition or conceptual embodiment previously disclosed in the prior art without providing sufficient guidance teaching how to make and use the claimed chimeric enzymes of the instant invention commensurate with a practical utility. Uncertainties concerning localization signals are only one small part of the larger problem directed at how to combine such signals to reduce the levels of carbohydrate or products for a practical, described purpose. Although the specification enables other chimeric molecules to be *produced* without undue experimentation, it does not enable production of chimeric molecules commensurate with the scope of the functional limitations recited in the instant claims and requirements under 35 U.S.C. 101. Although the specification enables the production of chimeric enzymes to reduce the levels of one specific xenogeneic Gal-α (1,3)-Gal epitope for the purpose of reducing hyperacute rejection, the specification fails to provide sufficient guidance teaching how to make and use any other nucleic acids encoding chimeric enzymes.

It is further noted that Applicants have failed to address the previous grounds of rejection directed at how to make and use the cells or "expression units" covered by claims 19-25 for ex vivo gene therapy or any other well-established use.

It would require undue experimentation for one skilled in the art to make and use the claimed invention. Applicants have failed to present any convincing arguments to rebut those set forth in the Office Action of 3/09/00 and have therefore failed to overcome the prima facie case for lack of enablement set forth therein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 8, 12-15, 17-20, and 23 remain rejected under 35 U.S.C. 102(a) as being clearly anticipated by Schwientek et al (J. Biol. Chem., 271(7):3398-3405, 1996).

Schwientek et al. disclose a gene fusion comprising a localization signal from the membrane anchor region of a yeast glycosyltransferase, Mnt1p, fused to the soluble form of human β-1,4-galactosyltransferase (see sentence abridging pp. 3398-3399), further comprising a

catalytic domain from the latter. One of the stated goals of the disclosure was to enable construction of yeast strains for that secrete desired glycoforms of applied proteins with limited production of mannose residues which are known targets for mannose-binding proteins and specific antibodies (p. 3399, left column, lines 10-13).

Applicant's arguments filed 11/06/00 have been fully considered but they are not persuasive. Applicants allege that the chimeric molecule described by Schwientek was made to enable expression of yeast β1,4-glycosyltransferase (Gal-Tf). The *purpose* or motivation for making the chimeric enzyme described by Schwientek is not germane to whether the composition anticipates the instantly claimed subject matter. Whatever, their original motivation may have been, Schwientek clearly teaches production of a chimeric glycosyltransferase relocalized to a different area of the cell to provide a means for outcompeting the native glycosyltransferase located in a more terminal processing compartment. This is clearly what was observed, given that the glycosyl chains of the fusion protein were shown to contain α1,6-, but not α1,3-mannose determinants (see e.g. abstract). Schwientek further characterized their approach as providing a strategy "to construct new yeast strains for that secrete *desired glycoforms* of applied proteins" (emphasis added; p. 3399, left column, lines 10-13) or to construct "mutants [to be] used as hosts for the synthesis of heterologous glycosyltransferases in an attempt to alter glycosyl structures" (p. middle of last paragraph, right column, p. 3404)--the very essence of the instantly claimed invention. Schwientek et al. conclude their disclosure by stating that their approach will allow [one] "to generate new host strains...that will allow the production of heterologous proteins,

whose glycosyl chains are modified by the addition of, for example, terminal Gal residues. These could be initially further modified in vitro by the addition of sialic acid (36) with the goal to shield mannose residues that are targets for mannose-binding proteins and specific antibodies" (p. 3404, last two sentences).

The response further argues that the last sentence of page 3403 does not directly lead to production of residues that are known targets for specific antibodies and that the process referred to therein is distinct from the process of directly using a chimeric enzyme, which comprises a heterologous sequence that enables the chimeric molecule to compete for substrate with another enzyme. These argument are not persuasive since the process referred to by Schwientek inherently involves production of mutant strains that employ the use of a chimeric enzyme that would allow that enzyme to outcompete other enzymes located in the same or more terminal processing compartments for those same substrates.

Claims 15 and 16 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sandrin et al (Xenotransplantation, 1:81-88, 1994).

Sandrin et al. disclose a cDNA clone for α-1,3-galactosyltransferase, pPGT-2, wherein the amino terminus comprises a localization signal (p. 82, last sentence abridging left and right columns and Fig. 1, p. 83).

Applicant's arguments filed 11/06/00 and amendment filed 11/20/00 have been fully considered but they are not persuasive. Applicants contend that the amendments to claims 15 and

16 render this rejection moot as the claims now more clearly define the claims' nucleic acid sequences which are not disclosed by Sandrin et al. This argument is not persuasive since the pPGT-2 clearly comprises an isolated nucleic acid molecule encoding a localization signal matching SEQ ID NO:12 as evidenced by Fig. 3, p. 85. Furthermore, the nucleic acid molecule disclosed catalyzes the production of an epitope reactive with an antibody to cause hyperacute rejection (see e.g. "Introduction", p. 81-82).

Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sandrin et al. (WO 94/21799).

Sandrin et al. (WO 94/21799) disclose an isolated nucleic acid molecule encoding a localization signal of a glycosyltransferase as set forth in SEQ ID NO:11 (i.e. MNVKGR; see p. 35. The disclosed nucleic acid comprises an amino terminus of gal-transferase, which catalyzes the production of an epitope reactive with an antibody to cause hyperacute rejection (see e.g. abstract).

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER